Synthesis of Suvorexant

Significance: Orexins A and B are excitatory neuropeptides that stimulate wakefulness. Suvorexant is a dual orexin receptor antagonist that is in phase III clinical trials for the treatment of insomnia. The key step in the asymmetric synthesis depicted is a tandem enzymatic transamination–annulation sequence ($F \rightarrow G \rightarrow H$).

Comment: A previous synthesis of suvorexant (N. A. Strotman et al. J. Am. Chem. Soc. 2011, 133, 8362) involved an asymmetric Ru-catalyzed reductive amination in the construction of the diazepane ring. The present route benefits from the circumvention of transition-metal catalysis and dichloromethane as solvent.